Health-related quality of life after myocardial infarction: methods for assessment and determinants

by

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Contents

Preface and acknowledgements

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Abbreviations

ACE-inhibitor	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
CABG surgery	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CCS Functional Classification	Canadian Cardiovascular Society Functional Classification
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
ECG	Electrocardiography
EQ-5D	EuroQol
HAD	Hospital Anxiety and Depression Scale
HF	Heart failure
HRQoL	Health-related quality of life
ICC	Intraclass correlation coefficient
INPHARM	INfarction and PHARMacotherapy
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MacNew QLMI	MacNew Quality of Life after Myocardial Infarction
MCS	Mental component summary
MI	Myocardial infarction
MLHF	Minnesota Living with Heart Failure Questionnaire
NHP	Nottingham Health Profile
NYHA Functional Classification	New-York Heart Association functional classification
OR	Odds ratio
PCI	Percutaneous coronary intervention
PCS	Physical component summary
RR	Risk ratio
SAQ	Seattle Angina Questionnaire
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36
SIP	Sickness Impact Profile
WHO	World Health Organization

List of papers

This thesis builds on the following papers:

Paper I

Pettersen KI, Reikvam Aa, Rollag A, Stavem K. Reliability and validity of the Kansas City Cardiomyopathy Questionnaire in patients with previous myocardial infarction. Eur J Heart Fail 2005; 7(2):235–42.

Paper II

Pettersen KI, Reikvam Aa, Stavem K. Reliability and validity of the Norwegian translation of the Seattle Angina Questionnaire following myocardial infarction. Qual Life Res 2005; 14(3):883–9.

Paper III

Pettersen KI, Reikvam A, Rollag A, Stavem K. Understanding sex differences in health-related quality of life following myocardial infarction. Int J Cardiol 2008; doi:10.1016/j.ijcard.2007.10.016.

Paper IV

Pettersen KI, Kvan E, Rollag A, Stavem K, Reikvam A. Health-related quality of life after myocardial infarction: the role of left ventricular function. Submitted to BMC Cardiovascular Disorders.

1 Introduction

1.1 Myocardial infarction

1.1.1 Definitions

The pathological definition of myocardial infarction (MI) is myocardial cell death due to prolonged ischemia [1]. This ischemia is almost always caused by a sudden reduction in coronary blood flow because of atherosclerosis with superimposed thrombosis, with or without concomitant vasoconstriction [2]. MIs are classified by (1) size – microscopic (focal necrosis), small (<10% of the left ventricle), medium (10–30% of the left ventricle) or large (>30% of the left ventricle), (2) localization – anterior, lateral, inferior, posterior, septal or a combination thereof, and (3) phase – acute (6 h to 7 days), healing (7–28 days) and healed (>28 days). Clinicians additionally classify MIs according to electrocardiography (ECG) criteria to determine if there is ongoing ischemia (ST-segment elevation, ST-segment depression or T-wave abnormality in two contiguous leads) or established MI (abnormal Q wave in the frontal plane leads or in leads V_4–V_6 and/or a QR wave longer than 30 ms in leads V_1–V_3). However, not all patients who develop myocardial necrosis exhibit ECG changes either acutely or chronically. In such cases the MI might be too small to produce ECG changes, or the changes are hidden within QRS confounders such as a bundle-branch block, left ventricular hypertrophy, Wolff-Parkinson-White syndrome or previous MI [1]. In everyday clinical practice, MIs are categorized according to ECG findings into ST-segment elevation and non-ST-segment elevation in the acute phase and into Q-wave MI and non-Q-wave MI in the subacute phase.

Since 2000, the clinical definition of acute or recent MI, in Norway and other countries, has been primarily based on biochemical markers of myocardial necrosis (Fig. 1) [1;3]. However, a previous definition of acute MI prevailed when the patients were included in the present study (Fig. 1) [4].

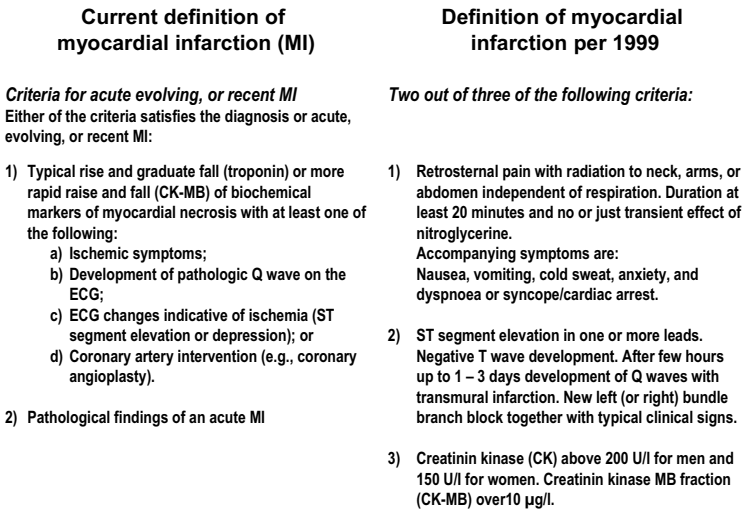

Figure 1 Current and previous clinical definitions of MI [1;3;4]

1.1.2 Epidemiology

Coronary artery disease (CAD) is a pandemic causing more than 7 million deaths each year, and thus is the most common cause of death worldwide [5]. While the number of deaths from CAD has declined in North America, Australia and many Western European countries over recent decades, there has been an analogously strong increase in death rates from CAD in many Eastern European countries. In addition, CAD is one of the most important causes of loss of future disability-free life as quantified by DALYs (disability-adjusted life years), and is in the same range as HIV infections, stroke and unipolar depressive disorders [6]. The World Health Organization (WHO) has estimated that CAD accounts for 10% of DALYs lost in low- and middle-income countries and 18% in high-income countries [5].

The number of deaths from cardiovascular diseases (CVDs) and MI is declining in Norway. Statistics Norway reported that approximately 20,100 people died annually from CVDs during the period 1971–1975, accounting for 51% of the total number of deaths, with this figure declining to approximately 17,400 annually for the period 2001–2003, accounting for 40% of the total deaths [7]. From 1996 to 2003 the number of patients who died from

acute MI also declined in Norway, from 5,771 in 1996 to 4,763 in 2003, accounting for 13% and 11% of the total deaths, respectively [8;9].

There are no reliable data on the incidence of MI in Norway. However, data from the Norwegian Patient Register, which records all hospital admissions, show that the number of admissions for acute MI declined by 18% between 1991 and 2000, from 14,457 to 11,892 [10], whereas the number of admissions among patients 80 years or older increased. New diagnostic criteria for acute MI were established in Norway in 2000 (Fig. 1), which resulted in the total number of hospital admissions for acute MI increasing by 33% between 2000 and 2002, to 15,829 [1;11].

Several factors make it difficult to establish the true natural history of an acute MI, including the high frequency of silent infarction, the high frequency of acute coronary deaths outside hospital and the diverse methods used to diagnose the condition. Community studies have shown that the overall mortality rate of acute heart attacks is 30–50% within the first month, with about half of these deaths occurring during the first 2 hours [12;13]. This high rate of initial mortality has changed only slightly during recent decades [14], whereas there has been a profound fall in the case-fatality rate amongst those treated in hospital. In the 1960s, the in-hospital mortality was about 25–30% [15]. In 1993, the in-hospital mortality was 18% in an unselected Norwegian MI population. In the present study, the in-hospital mortality of our patients recruited in 1999 from the same hospitals as in 1993 plus a few additional hospitals was 15% [16;17]. Two recent publications from the Worcester Heart Attack Study stated that while in-hospital deaths after MI decreased from 20% between 1975 and 1978 to 12% in 2001, the 1-year crude case-fatality rate of patients discharged alive after MI increased from 14% between 1975 and 1978 to 20% in 2001 [18;19]. However, after adjusting for age, sex and cardiovascular comorbidity, the increase was not statistically significant [19].

From 4% to 12% of the decline in CAD mortality rates has been attributed to the initial treatment of MI, while 23–46% of the decline being attributed to all medical and surgical therapies [20-23]. The WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project monitored trends in CAD over 10 years in 21 countries. In MONICA populations in which CAD mortality decreased, reduction in coronary events were responsible for two-thirds of the decrease, with reduction in case fatalities accounting for the other third [13]. While mortality from CAD has declined, the number of hospital admissions has increased, which is mainly due to chronic manifestations of CAD producing a growing population of patients whose lives are affected by symptomatic CAD [24].

1.1.3 Sequelae after MI

MI patients are at risk of subsequently experiencing one or more sequelae such as malignant arrhythmias, reduced left ventricular function, angina pectoris and psychological reactions, particularly depression. Patients are at a high risk of sudden cardiac death due to malignant ventricular arrhythmias within 1–2 years of an MI [25]. Two patterns of fatal arrhythmias have been identified in patients with ischemic heart disease: (1) ventricular tachyarrhythmias triggered by acute myocardial ischemia in patients with or without preexisting myocardial scarring, and (2) ventricular tachyarrhythmias related to an anatomical substrate (usually scarring from a previous infarction) without active or clinically evident myocardial ischemia [26]. Epidemiological data suggest that 80% of fatal arrhythmias are caused by structural arterial abnormalities and their consequences [26].

Reduced left ventricular function and overt heart failure (HF) due to the loss of viable myocardial tissue are common consequences of MI, but in some patients HF is caused by acute mitral regurgitation, arrhythmias, cardiac stunning or diastolic dysfunction of the left ventricle [27]. The presence of left ventricular dysfunction or HF indicates a graver prognosis, even when it presents only transiently [27]. A recent review found that 30–40% of acute-MI patients experience HF at some time following hospital admission for the MI [28]. This is in accordance with estimated numbers in a UK study [27]. In a study including all patients with MI in a community from 1979 to 1998, 41% of the patients without previous chronic HF experienced episodes with HF [29]. Among patients experiencing episodes of HF after their MI, 59% had their episodes within the first 30 days after the MI, 9% within the next 11 months, and 32% thereafter [29]. The median survival in patients who experienced episodes of HF was 4 years, and this did not improve for patients included during the last years of inclusion compared with patients included earlier, even after adjustment for baseline characteristics [29]. Also, the Worchester Heart Attack study found that the mortality rate was 50% higher in patients with known chronic HF and in those who had HF as a complication to the index MI [19]. On the other hand, in the Framingham study 5-year case fatality from HF independent of aetiology, decreased in both men and women from 70% and 57 % respectively in 1950 – 69 to 59% and 45% in 1990-99 [30].

There is less information on the prevalence and incidence of left ventricular systolic dysfunction after MI without manifest HF. A French MI-register study revealed that 52% and 46% of patients had a left ventricular ejection fraction (LVEF) of ≤50% within 5 days of an

MI in 1995 and 2000, respectively [28]. Screening data from clinical trials performed during 1990–2002 showed that approximately one-third of MI patients had an LVEF of ≤40% during the first week after MI [28]. Left ventricular systolic dysfunction observed after an MI is one of the most important predictor of mortality following MI. The GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) study found that the 6-month mortality was almost 10-fold higher in patients with an LVEF of <40% (60 out of 569 patients died) than in patients with an LVEF of ≥50% (18 out of 1672 patients died) [31]. This difference had not changed since the prethrombolytic era, emphasizing the importance of interventions aimed at minimizing left ventricular damage [32].

Whilst the LVEF is inversely correlated with the risk of developing HF after MI, there is evidence that left ventricular systolic dysfunction and the occurrence of HF are both independent predictors of mortality after MI. One study found that the 1-year all-cause mortality in patients with in-hospital HF after MI was 8% in patients with a normal LVEF, 19% in patients with an intermediate LVEF and 26% in patients with a reduced LVEF, while the corresponding numbers for the same LVEFs were 3%, 6% and 12%, respectively, in patients without in-hospital HF after MI [33].

Chest pain or angina pectoris is the core symptom of CAD. The prevalence of angina pectoris in Western countries is estimated to be 2–4% in people aged 45–74 years, but these estimates are based largely on studies performed between 1970 and 1985 [34]. The GUSTO-I (Global Utilization of Streptokinase and t-PA for Occluded coronary arteries) trial found that the incidence of in-hospital post-infarction angina pectoris was 20% [35]. One study found that 56% of men and 63% of women had experienced chest pain during heavy physical exercise within 1 year of an MI, with 21% and 28% experiencing chest pain at rest [36]. In a follow-up study that applied the Rose angina questionnaire [37], 22% of patients reported angina and only 44% reported no chest pain within 4 years of an MI [37;38]. The patients in these two studies had their index MI 13 to 20 years ago [36-38]. The annual mortality rate in patients with stable angina pectoris has been estimated from clinical trials at 0.9–1.4% [34]. This is in accordance with registry data indicating an annual cardiac mortality rate of 1.5% in stable, medically treated patients with CAD [39]. However, the death rates were two- and fivefold higher in patients with one and more than one previous MI, respectively, than in those with no previous MI [39].

Approximately 20% of patients experience major depression after MI, with another 20% experiencing minor depression [40]. Two recent meta-analyses concluded that both the short- and long-term total mortality is higher in depressed patients with MI or CAD than in

non-depressed patients [41;42]. The mechanism underlying this increased mortality is unclear, but theories include both biological and behavioral mechanisms, such as cardiotoxicity of antidepressant drugs, more major cardiac risk factors, more severe coronary disease in depressed patients, reduced adherence to medical treatment, altered cardiac autonomic tone, greater platelet activation, inflammatory processes and an unhealthy lifestyle, including physical inactivity, unhealthy diet and smoking habits [43;44]. It is not known whether treating depression in patients with CAD will improve cardiovascular outcomes. However, treatment is important in order to relieve psychological, social and functional impairments [44].

1.1.4 Interventions

During the last 2–3 decades, several new medical and surgical interventions have increased survival and function in patients with MI. Beta blockers limit the infarct size, reduce life-threatening arrhythmias and relieve pain in patients with acute MI [45]. A meta-analysis of 82 trials showed that beta blockers did not reduce all-cause mortality within 6 weeks after an MI (odds ratio (OR)=0.96, 95% confidence interval (CI)=0.85–1.08) but did significantly reduce long-term all-cause mortality (OR=0.77, 95% CI=0.69–0.85) [46], with the effect being highest in patients older than 65 years [47].

Platelets are important in the formation of the thrombus that is superimposed on the atherosclerotic plaque in an acute MI. Currently available antiplatelet drugs, such as acetylsalicylic acid and clopidogrel, interfere with certain steps in the activation process of platelets, including adhesion, release and/or aggregation, and thus prevent the formation of the thrombus [48]. A meta-analysis of patients with an acute MI showed that 1 month of antiplatelet therapy reduced the incidence of vascular events (MI, stroke or vascular death) by 38 (standard error (SE)=5) (p<0.0001) per 1000 treated patients, and total mortality by 24 (SE=4) (p<0.0001) per 1000 treated patients [49]. In patients with previous MI with a mean treatment duration of 2 years, the corresponding mean reductions were 36 (SE=5) (p<0.0001) per 1000 treated patients for all vascular events and 12 (SE=5) (p=0.02) per 1000 treated patients for total mortality [49].

Thrombolytic therapy in acute MI aims at restoring coronary flow by recanalizing the thrombotic occlusions associated with the MI and thereby reducing the infarct size, improving in myocardial function and in the chances of survival. Thrombolytic therapy is indicated in MI patients with ST-segment elevation or newly developed left-bundle-branch

block (without contraindications) presenting within 12–18 hours of symptom onset [4]. A systematic review of the effect of thrombolytic treatment on mortality in nine trials, each of which included more than 1000 patients with suspected MI, revealed highly significant reductions in 5-week mortality of 30 per 1000 treated patients in patients presenting within 0–6 hours after onset and of 20 per 1000 in patients presenting within 7–12 hours, and a statistically uncertain reduction of 10 per 1000 in those presenting at 13–18 hours after onset [50]. An analysis of the 10-year survival of the ISIS-2 (Second International Study of Infarct Survival) patients found that early survival advantages produced by thrombolytic therapy in acute MI were maintained for at last 10 years [51].

Percutaneous coronary intervention (PCI) is the process of catheter mediated angioplasty, usually with a balloon, in a narrowed or occluded coronary blood vessel with or without the placement of a stent. Randomized clinical trials in MI patients with ST-segment elevation comparing timely preformed primary PCI (e.g. intervention in the culprit vessel within 12 h after the onset of symptoms) with thrombolysis have shown more effective restoration of patency, less reocclusion, improved residual left ventricular function and better clinical outcome [52]. In a meta-analysis of 23 randomized trials primary PCI was more effective than thrombolysis in preventing short time death (7% vs. 9%, p=0.0002) and non-fatal reinfarction (3% vs. 7% p<0.0001) and the results persisted during long-term follow-up [53]. Routine coronary stent implantation in patients with acute myocardial infarction decreases the need for target-vessel revascularization but is not associated with significant reductions in death or reinfarction rates when compared with primary angioplasty [52]. Also in patients with non-ST-segment elevation acute coronary syndrome (ACS) early coronary angiography including PCI when possible and indicated is beneficial compared to selective performance of angiography based on clinical course [54]. A meta-analysis of the most contemporary trials has confirmed this showing a long-term benefit in terms of both death (RR (risk ratio) 0.75 CI 0.62–0.92) and new MI (RR 0.75 CI 0.62–0.91) [55].

Coronary artery bypass graft surgery (CABG) prevents death, irreversible myocardial damage and malignant arrhythmias, and relives angina symptoms. These benefits have been documented in patients with main left coronary artery stenosis, in patients with significant stenosis in the proximal part of the left anterior descending artery and one other segment of the other coronary artery domains and when one or more segment are affected in all three coronary artery domains [56-58].

Angiotensin-converting enzyme (ACE) inhibitors competitively block conversion of angiotensin-I into angiotensin-II and reduce the breakdown of bradykinin, producing

haemodynamic, neurohormonal, antiproliferative, natriuretic and antiatherogenic effects, many of which are important when treating patients with CAD and HF [59]. There have been two types of studies of ACE inhibitors in MI: (1) early-intervention trials, with initiation of ACE inhibitors within 24–36 hours after the MI, and (2) late-intervention trials, with initiation later than 48 hours after the MI.

A meta-analysis including patients from the early-intervention studies revealed that the 30-day mortality was lower for treated patients than placebos (7.1% vs. 7.6%) (p<0.004) equaling 5 lives saved per 1000 patients treated for 4–6 weeks [60]. This was due to a more pronounced effect in patients presenting with HF or anterior MI. Early treatment with ACE inhibitors also protected against non-fatal HF after the MI (14.6% vs. 15.2%) (p=0.01) [60].

Late-intervention studies have included patients with a reduced LVEF or HF, who constitute a high-risk group. A meta-analysis of these studies with a mean follow-up of 2.6 years revealed a reduction in mortality compared with placebos (23.4% vs. 29.1%), corresponding to 57 deaths prevented per 1000 patients treated for 2.5 years [61]. Secondary prevention after MI in patients without HF has also been studied. Two of the largest studies, HOPE (Heart Outcomes Prevention Study) and EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in stable Coronary Artery Disease), found that the primary end points (HOPE: death from cardiovascular causes, MI or stroke; EUROPA: cardiovascular mortality, MI or sudden death) were reduced by 38 per 1000 patients treated for 5 years in the HOPE study and by 50 per 1000 patients treated for 4.2 years in the EUROPA study [59].

The 4S study (Scandinavian Simvastatin Survival Study) was the first to clearly demonstrate the benefits of statins after MI [62]. In the 4S study, the mortality was lower in patients treated with statins than in controls (8% vs. 12%), corresponding to 33 lives saved per 1000 patients treated for 5.4 years [62]. A recent meta-analysis showed that the effect of statins on major vascular events was proportional to the achieved reduction in LDL cholesterol [63]. The PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study also has shown the benefit of statins in the elderly [64]. In patients aged 70–82 years, the composite end point of coronary death, non-fatal MI and stroke was reduced in patients with known CVDs compared to controls (17% vs. 22%), corresponding to a reduction of 43 events per 1000 patients treated [64].

1.1.5 Outcomes in MI

The ultimate and traditionally used measure of outcome in cardiovascular research is cardiovascular and total mortality. Composite end points such as mortality plus events or event-free survival have also been used, especially when a low mortality rate is expected. Events other than death can include both cardiac and cerebrovascular incidents, and sometimes also hospitalization due to deterioration of a chronic condition. The observed decrease in cardiovascular mortality and increase in admission rates for chronic conditions such as HF and CAD suggests that the longer survival of patients with heart diseases contributes to a growing population of patients at increased risk of subsequent cardiovascular complications [24]. This group of patients needs to be evaluated with outcome measures other than mortality alone in clinical trials, epidemiological research and other observational studies. Possible outcomes other than death include return to work, the New York Heart Association (NYHA) Functional Classification, chest pain on the Canadian Cardiovascular Society (CCS) Functional Classification, functional status, and measures of health status and quality of life [65;66]. The European Society of Cardiology has included maintenance and improvement of quality of life as treatment goals in their guidelines, both for patients with chronic HF and those with stable angina pectoris [34;67].

1.2 Health-related quality of life

1.2.1 Concepts and definitions

In 1948 the WHO defined health as "…a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity" [68]. The concept of quality of life lacks a formally agreed definition, but it is clearly complex, abstract and multidimensional. Quality of life is distinct from (but related to) health, and many attempts to define quality of life have been based on the WHO definition of health [69;70]. The quality of life assessment group of the WHO defines quality of life as "the individual's perception of their position in life in context of the culture and value system in which they live and in relation to their goals, expectations, standard, and concerns" [71]. Other published definitions include "…those aspects of life and human function considered essential for living fully" [72] and "…an individual's satisfaction with life in domains he or she considers important" [73]. It is clear that quality of life means different things to different people, and has different meanings depending on the area of application. Some have argued that, at least in Western

countries, people intuitively understand the factors influencing quality of life, and thus no formal definition is needed [69].

Attempts to distinguish between quality of life in the more general sense (often referred to as the overall quality of life) and quality of life related to the requirements of clinical medicine and medical research have led to the introduction of the "health-related quality of life" (HRQoL) [69]. Several definitions of HRQoL have been proposed. A popular definition is that by Wenger and Furberg [74]: "Those attributes valued by patients, including: their resultant comfort or sense of well-being; the extent to which they are able to maintain reasonable physical, emotional, and intellectual function; and the degree to which they retain their ability to participate in valued activities within the family, in the workplace, and in the community." A consensus conference in the early 1990s agreed upon the fundamental dimensions essential to HRQoL assessment [75]. As primary dimensions they suggested physical functioning, social functioning, psychological functioning, overall life satisfaction/well-being and perception of health status, with additional dimensions including intimacy, sexual functioning, sleep disturbance, pain and symptoms.

The term health status refers to the level of wellness and illness, taking into account the presence of biological or physiological dysfunction, symptoms and functional impairment. Bergner distinguished between health status and quality of life [76], although health status is often used interchangeably with HRQoL [70].

1.2.2 Measures for assessing HRQoL

One of the main interests in this field has been developing measurement instruments [77]. There are three principal types of HRQoL measures: generic, disease-specific and domain-specific instruments [69;78]. Generic instruments are meant for general use, irrespective of the illness or condition of the patient, and often are also applicable to healthy people [69]. The advantage of generic instruments is that scores can be compared across different patient groups and with general-population norms. Generic instruments are supposed to cover the main dimensions of HRQoL and commonly include items that explicitly inquire about the overall quality of life [69].

Disease-specific instruments cover all or most of the main dimensions of HRQoL whilst focusing on the issues of particular concern to patients with specific diseases or groups of diseases. The criteria used to assess outcomes vary between diseases. Disease-specific

HRQoL instruments are needed to ensure sensitivity to small but clinically significant changes in health status and to levels of disease severity [78].

Domain-specific instruments are instruments that explore particular issues in greater depth without aiming to cover all the main dimensions of HRQoL [69;78], such as pain, depression, anxiety, fatigue and coping.

1.2.3 Properties of HRQoL instruments

Transferring an HRQoL instrument from one country to another with a different language and culture requires formal translation and adaptation, which can be accomplished in several ways. One recommended process is to first translate and back-translate the instrument according to an accepted procedure, and then test an agreed translation in the new environment [79;80]. This elaborate translation process aims to avoid introducing errors into the questionnaire or shifts in nuances that might affect the way patients respond to items, with the subsequent test designed to show that the translated version is equivalent to the original instrument.

1.2.3.1 Reliability

The reliability of a measurement instrument refers to the extent to which it yields the same result on repeated trials [81]. Reliability in HRQoL studies can be assessed in different ways. First, the test–retest reliability refers to the extent to which an instrument gives the same score when applied at different times, on the assumption that the quality of life of investigated individual has not changed in the intervening periods [81]. It is also used to refer to whether the measurement tool gives the same results when administered to two individuals with the same HRQoL. The test–retest design produces relevant information on instrument reliability when it is likely that the characteristics of the person being assessed have not changed. Conventionally, to minimize recall bias, reliability is assessed using a test and retest separated by up to 4 weeks.

Second, the internal consistency reliability refers to the degree of homogeneity of items in an instrument or scale. This denotes the extent to which responses to the various components of the instrument correlate with one another or with a score on the instrument as a whole (either including or excluding the items in question). The presence of a strong correlation between these elements suggests that they are measuring the same or closely

related constructs in a reliable manner, whereas a weak correlation suggests that the construct is not being measured reliably and that there are sources of unexplained error in the measurement. Internal consistency reliability is most often quantified using Cronbach's alpha [80-82].

The minimal levels of reliability considered necessary vary with the specific application. As a general rule, reliabilities should be at least 0.80 for widely used scales [81], with the reliability and precision of the measurement increasing when the decision is more critical [79;80].

1.2.3.2 Validity

The validity of a measurement instrument does not refer to the instrument itself, but to whether particular interpretations of its scores are well-justified. It is only meaningful to consider the validity of a specified purpose or interpretation of the resulting scores. The inferences that may be made from the score for a given instrument vary with the situation in which it is applied, and hence the validity of each inference must be established [83].

An overall assessment of the utility and limitations of a measurement instrument is gradually built up from cumulative evidence about interrelationships among the content of the instrument and definitions of the construct to be measured, and interrelationships among scores and results of other relevant measurements. Typically, this process involves comparisons of measurements made in cross-sectional and longitudinal studies, frequently before and after a certain intervention.

Some authors have divided validity into three distinct categories, as listed below, while others have considered many different attributes, and the terminology is diverse [80]. Distinguishing between different types of validity is often not useful, and so validation can be considered a process of hypothesis testing without the traditional division into distinct types of validity [80]. However, the various types of validity all address the degree of confidence that can be placed on inferences drawn from scores obtained on scales [80].

We now present a traditional typology of validity, content validity, construct validity and criterion-related validity, based on several previous reports [69;80;81]. Content validity is the extent to which the items in the instrument are linked by a plausible rationale to some particular conception of the construct being measured, such as the quality of life. This is normally based on the judgment of the developers, experts or users of the instrument.

Construct validity comprises several types of validity. Information on the internal statistical structure of an instrument is relevant to the interpretation of its scores. Other types of evidence sought include relationships of scores with other variables. Evidence supporting particular interpretations may come from findings of similar results (convergence) or dissimilar results (divergence), depending on the variables involved.

For HRQoL instruments, it is frequently assumed that a more severe disease is, on average, associated with a lower quality of life. Similarly, it can be expected that a treatment that is already known to reduce the severity of a disease or its symptoms will be associated with an improved quality of life [83].

Hence, correlations between scores on an HRQoL instrument and variables representing other clinical indicators such as use of medication, reported chest pain or the LVEF might be examined. Alternatively, differences in HRQoL scores can be compared between treated and untreated subjects. It is expected that, on average, scores on the HRQoL instrument will be correlated with or show differences or changes in the expected direction in concert with clinical markers or disease severity and with other health status measures [83].

Criterion-related validity represents evidence of validity by showing relationships between scores and criterion variables. Selecting a single criterion variable as a gold standard is difficult for quality of life instruments, due to the subjective nature of the construct. If the criterion variable exists at the same time as HRQoL is measured, the criterion validity is called concurrent validity. Predictive validity, on the other hand, refers to a future criterion [81]. Validating an instrument is an ongoing process since a single relationship is normally insufficient to conclusively establish the validity of a given interpretation.

1.2.4 Theoretical models linking biochemical, physiological and clinical variables with HRQoL

A conceptual model is needed as a foundation for the construct of HRQoL and to explain the relationships among these components [77]. A sound theoretical model would assist the selection of measures for use in clinical studies by allowing the critical evaluation of both the validity and usefulness of the instruments. A clear theory would also allow hypotheses about the relationship between patient characteristics, the intervention and the outcome to be tested, so as to detect possible confounding. A theoretical model would also facilitate the use of HRQoL measures as a primary outcome by allowing specific hypotheses to be made about which components of the model are expected to respond to interventions [77].

Some work has already been done in this field. Wilson and Cleary have presented a theoretical framework linking HRQoL with clinical variables [70]. This model, presented in Fig. 2, suggests that health exists on a continuum with of increasing, social and psychological complexity. Each step in the model from symptom status is again affected by characteristics and environment of the individual patient.

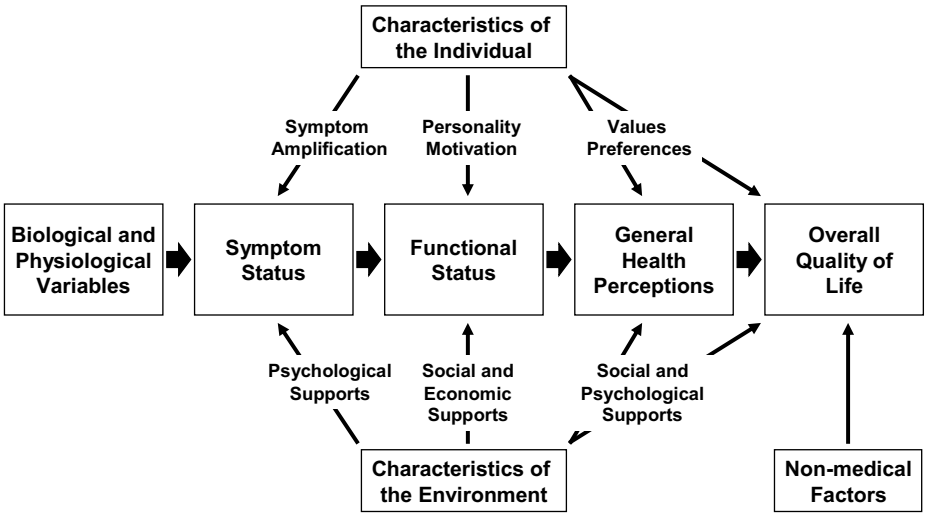

Figure 1 Conceptual model relating HRQoL with other patient outcome measures. From Wilson and Cleary [70]

For heart patients, biological and physiological variables include results from clinical examinations, including auscultation of the heart, laboratory results including serum markers of cardiac damage, echocardiographic parameters, other cardiac imaging techniques and ECG. Symptoms are the perceptions of patients of an abnormal physical, emotional or cognitive state [70]. Cardinal symptoms of heart disease include chest pain or discomfort, syncope, collapse, palpitation, dyspnoea, oedema, cough, haemoptysis and excess fatigue

[84]. Emotional symptoms such as anxiety and depression are also often associated with cardiac diseases [36].

Functional status is the ability of an individual to perform normal daily activities, fulfill usual roles, and maintain health and well-being [70;85]. The two most used functional scales in cardiovascular patients are the CCS Functional Classification, which assesses function in relation to chest pain, and the NYHA Functional Classification, which assesses function in relation to any symptom related to the cardiovascular system (e.g. fatigue, palpitation, dyspnoea or chest pain) [65;66]. Four commonly measured domains of functioning are physical, social, role and psychological [70].

General health perceptions represent the integration of all the above-mentioned health concepts as well as others such as mental health, and they are by definition subjective ratings [70]. General health perceptions have been found to be strongly correlated with the use of general medical services, somatization and hypochondrias [70;86]. However, the concept has also been found to be a strong predictor of survival. One example is a study on 10-year survival in patients with MI, CABG surgery or PCI, which found that the score for subjective general health 1 year after the index event was the strongest predictor of death within 10 years, with a risk ratio >3 when the score differed by 1 on a scale from 1 to 4, which is about twice that of any other dimensions of quality of life [87].

Overall quality of life is assumed to represent a stable synthesis of a wide range of experiences and feelings that people have. As such it should be related to HRQoL and to other salient life circumstances, experiences and feelings [70]. However, the correlation between overall quality of life and objective life status is weaker than anticipated, which might be due to accommodation to illness, changes in internal standards or values, or to conceptualization of the overall quality of life catalyzed by a change in health state [88;89].

1.3 HRQoL after MI

1.3.1 Assessment of HRQoL in patients with MI

The most commonly generic instruments applied to patients with MI are the Sickness Impact Profile (SIP), the Nottingham Health Profile (NHP), and the Short Form 36 (SF-36) and its shorter versions the SF-12 and SF-8 [90-95]. An assessment of patients with CAD using the SIP, NHP and SF-36 concluded that the SF-36 was the most reliable, valid and sensitive

instrument for assessing the quality of life [96]. Both the SF-36 and SF-12 have shown high validity and reliability in patients with CAD [97;98]. The EuroQol (EQ-5D) index has also shown high validity and reliability in CAD patients, and is increasing in popularity [99-101].

Some of the most commonly used disease-specific HRQoL instruments for MI, angina or HF in recent years have been the MacNew Quality of Life after Myocardial Infarction questionnaire (MacNew QLMI), the Seattle Angina Questionnaire (SAQ), the Minnesota Living with Heart Failure Questionnaire (MLHF) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) [102-106]. All of these instruments have documented validity and reliability [106;107]. However, a direct comparison revealed that angina grades could be discriminated better with the MacNew QLMI questionnaire than with the SAQ, although the SAQ was more responsive to longitudinal changes over time [108]. Moreover, the KCCQ has been found to be more responsive to changes than the MLHF [106].

1.3.2 Effect of MI on subsequent HRQoL

A systematic review of the quality of life after MI concluded that HRQoL is minimally affected by an MI [109], although the authors stated that this might have been due to the measurement tools not being sensitive enough. Moreover, this result contrasts the findings in population-based studies [110-112]. One such study measured HRQoL in the same population over a 5-year interval, during which 62 of 10 618 subjects developed CAD (60% unstable angina or MI) [102]. The decline in HRQoL between the two measurements was significantly more pronounced in subjects who developed CAD than in 310 controls without CAD on four out of eight SF-36 scales. In another population-based study, 89 of 8 723 patients developed MI, and measures of HRQoL using a specially designed instrument showed that premorbid HRQoL in patients who later developed MI was comparable to the age-adjusted population norms [112]. Three assessments of HRQoL during the 12 months immediately following the MI revealed a monotonic decrease in HRQoL. The changes were most pronounced for physical functioning, but statistically significant also for social functioning, role functioning, anxiety and depression symptoms. In a third study, patients 65 years or older underwent repeated measurements of HRQoL [111]. Patients who had an MI between the measurements were more likely to experience a decline in HRQoL. Several studies also found that HRQoL scores still were lower from 1 to 5 years after the MI than general-population norms based on both the SF-36 and the NHP [38;113-115].

In a study comparing HRQoL between different patient groups, the SF-36 scores in patients with cardiovascular conditions were comparable to those in patients with cancer, endocrine diseases, visual impairments and chronic respiratory diseases, but not as bad as those in patients with gastrointestinal conditions, cerebrovascular/neurological conditions, renal diseases or musculoskeletal conditions [116]. When comparing between different cardiovascular diagnoses, the impairment in HRQoL was reportedly greater in patients with HF than in patients with other heart conditions such as angina pectoris and those with a history of MI [112;117].

1.3.3 Determinants of HRQoL after MI

A review of the quality of life after MI based on literature published between 1985 and 1999, which included 11 studies that assessed HRQoL from 4 months to 5 years after the index MI [109], found that the severity of MI-related symptoms, the age of the patient and the timing of HRQoL measurement after MI had the greatest effects on HRQoL after MI. Subsequent studies using the SF-36 or SF-12 have identified employment status, symptoms, manifestations of CAD other than MI, additional comorbidity, depression and baseline HRQoL as important determinants of later HRQoL [114;115;118-121].

Whether sex is a determinant of HRQoL after MI remains debatable, given that several studies have demonstrated a sex difference in HRQoL after MI while others have not [36;114;115;118;119;121-130]. Also, one study found that social support was an important determinant for HRQoL in patients with angiographically verified CAD [131].

The identified determinants vary between studies due to differences in patient selection, time interval between MI and the survey of HRQoL, the potential predictors included and the chosen measures of HRQoL.

2 Aims of the study

The long-term course of MI has changed in recent decades, with a substantially increased survival leading to the need for additional outcome measures in patients with MI. HRQoL has proved useful for measuring the outcome after MI when following up patients with CAD. A better understanding of HRQoL in cardiac diseases is crucial, as is the need for adequate and well-functioning instruments to measure HRQoL in these diseases.

The overall objective of the present study was to contribute to increased use of HRQoL measures in clinical practice and cardiologic research through cultural and language adaptation of instruments, assessment of their psychometric properties and improved understanding of HRQoL following MI. To achieve this overall objective, the study had the following secondary goals:

1. To translate and adapt a short questionnaire for patients with impaired heart function for use in Norwegian patients.
2. To assess the reliability and validity of this questionnaire in patients with prior MI.
3. To assess the reliability and validity of a short angina pectoris-specific questionnaire in Norwegian patients with prior MI.
4. To compare HRQoL in patients 2.5 years after MI with an age- and sex-adjusted Norwegian general population.
5. To compare HRQoL 2.5 year after MI between men and women.
6. To identify determinants for HRQoL 2.5 years after an MI in men and women separately.
7. To assess the association of the LVEF measured during hospitalization for the index MI with subsequent HRQoL.

3 Study design and methods

This study was based on a prospective observational cohort study including a cross-sectional postal survey of patients with previous MI recruited to the INfarction and PHARMacotherapy (INPHARM) study.

The official clinical diagnoses were accepted without reassessment or revision. We used the following definition of MI [4]:

1. Retrosternal pain with radiation to neck, arms or abdomen, independent of respiration. Duration at least 20 minutes and no or just transient effect of nitroglycerine. Accompanying, symptoms are: nausea, vomiting, cold sweat, anxiety, and dyspnoea or syncope/cardiac arrest.
2. ST segment elevation in one or more leads. Negative T-wave development. After few hours up to 1–3 days development of Q-waves with transmural infarction. New left (or right) bundle branch block together with typical clinical signs.
3. Creatinin kinase above 200 U/l for men and over 150 U/l for women. Creatinin kinase MB fraction over 10 microg/l.

3.1 Data collection

3.1.1 The INPHARM study

The INPHARM study included patients with a discharge diagnosis of acute MI, defined as codes I21 and I22 in the ICD-10 (The International Statistical Classification of Diseases and Related Health Problems, tenth version). The INPHARM study included consecutive patients discharged alive or dead from 16 hospitals during 3- to 6-month periods between August 1999 and January 2000. Patients who were dead before admission to the casualty department or who died before receiving any medical treatment, and patients who had their infarct during hospitalization for other conditions, were not included in this study. The following hospitals participated in the INPHARM study: Aker University Hospital, Oslo; Akershus University Hospital, Lørenskog; Diakonhjemmet Hospital, Oslo; Haugesund Hospital, Haugesund; Innlandet Hospital, Elverum; Innlandet Hospital, Gjøvik; Innlandet Hospital, Hamar; Innlandet Hospital, Kongsvinger; Innlandet Hospital, Lillehammer; Innlandet Hospital,

Tynset; Levanger Hospital, Levanger; Lovisenberg Diakonale Hospital, Oslo; Nordland Central Hospital, Bodø; Ullevål University Hospital, Oslo; Vestfold Hospital, Tønsberg; and Ålesund Hospital, Ålesund. A total of 901 patients were included in the study.

One or two local cardiologists recorded a structured data set from the patient medical records. The data set included information on the medical history, presenting features, drugs used before admission, smoking habits, the LVEF measured during hospitalization, treatment received during hospitalization and drugs used at discharge. Cardiovascular drugs used at discharge were classified into the following 11 classes: aspirin, beta-blockers, regular nitrates, diuretics, calcium antagonists, ACE inhibitors, warfarin, digitalis, statins, angiotensin-II receptor antagonists and ticlopidine/clopidogrel. The indications for use were classified as secondary prevention, hypertension, angina pectoris, HF or other. The LVEF was classified as >50%, 40–50% and <40%. The data are presented in Appendix I. A physician collected the data within 6 months of hospital discharge.

3.1.2 The postal survey

At a mean of 2.5 years (range 2.1–3.1 years) after the index MI, we mailed a questionnaire to patients who were alive (according to the hospital information system and the national population register of Statistics Norway). Questionnaires were sent to the patients from the hospitals where they were discharged, with a cover letter signed by the head of the cardiology unit of the hospital. After 4 weeks we sent a reminder to non-respondents.

3.1.3 Formal requirements

The physicians collected the INPHARM study data after discharge to avoid interference with patient treatment. The Norwegian Data Inspectorate approved the establishment of the INPHARM database and gave a concession for the data to be used for 10 years. The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate also approved the postal survey (Appendix II). The patients agreed to participate in the survey by responding to the questionnaire.

We entered no personal identifiers into the databases. However, each head physician at the participating hospitals kept a paper list that linked the serial number in the study with information that identified each person.

3.1.4 The questionnaire

The questionnaire consisted of several sections. In addition to HRQoL instruments, we asked about work status, cardiovascular events after the index MI, smoking habits and current medication. The HRQoL instruments included in the questionnaire are described below. The questionnaire is detailed in Appendix III.

3.1.4.1 SF-36

The SF-36 is a generic 36-item health status questionnaire that reports HRQoL on the following eight scales: Physical functioning, Role functioning-physical, Bodily pain, General health, Vitality, Social functioning, Role functioning-emotional, and Mental health [92-94]. The raw scores on these scales are transformed to a score from 0 to 100, with a higher value indicating a better level of functioning. The eight SF-36 scales are weighted and aggregated to two summary scales: the Physical component summary (PCS) and the Mental component summary (MCS) [132]. The PCS and MCS scores are reported on a standardized scale for comparison with a general US population with a mean score of 50 and a standard deviation (SD) of 10 [132]. The SF-36 has been extensively validated and used in patients with CAD [38;92;96;97;133-135]. We used the Norwegian standard SF-36, version 1.2 [136].

3.1.4.2 EQ-5D Index

The EQ-5D is a generic HRQoL instrument consisting of five items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item is scored on 3-point scale: no problems (score of 1), moderate problems (2) and extreme problems (3). Responses to these items can be converted to a utility score, the EQ-5D Index, by applying time trade-off valuations obtained from the general population to each of the possible five-dimensional health state profiles. A score of 1.0 represents perfect health and 0 represents being dead (negative utilities are also possible, representing states perceived to be worse than being dead). We used a time trade-off tariff from a representative sample of the UK population [137]. The EQ-5D Index has high validity in post-MI patients [99;138;139].

3.1.4.3 KCCQ

The KCCQ is a 23-item questionnaire measuring HRQoL in patients with chronic HF regardless of aetiology [106]. Each item is scored on a 5-, 6- or 7-point scale [80]. The questionnaire assesses the following six domains of HRQoL: Physical limitation, Symptoms, Symptom stability, Social limitation, Self-efficacy and Quality of life. We calculated the score on each scale as the mean of the item scores, which was then transformed to a score from 0 to 100, with a higher score indicating a higher level of functioning. In addition, the KCCQ scales were aggregated into two summary scores: the Functional status summary score (the mean of the Physical limitation- and the Symptoms scale scores) and the Clinical summary score (the mean of the Physical limitation-, Symptoms-, Social limitation- and Quality of life scale scores) [106].

The culture and language of the KCCQ was adapted using a recommended procedure [79]. Two persons independently translated the questionnaire into Norwegian, with agreement on a consensus version reached after discussion with a third person. This version was then back-translated into English by a professional translator. Comparison of the back-translated version with the original English version revealed only minor discrepancies which were rectified.

3.1.4.4 SAQ

The SAQ is a 19-item questionnaire measuring HRQoL in patients with CAD. The questionnaire assesses the following five domains of HRQoL: Physical limitation, Angina stability, Angina frequency, Treatment satisfaction, and Disease perception. Items are scored on 5- or 6-point scales. Each score on the five scales is calculated as the sum of item scores in the domain, which is then transformed to a score from 0 to 100 (with a higher score indicating a better level of function) by subtracting the lowest possible score, dividing by the range of the scale and multiplying by 100 [103]. The SAQ has been shown to be valid, reliable and sensitive [103;134;140]. It has been used to assess outcomes in clinical trials, predict events, measure quality of care and support patient management [141-145]. The questionnaire was translated using a recommended translation/back-translation process [79].

3.2 Description of the material

The material in the postal survey of the INPHARM study is presented in Fig. 3. One of the hospitals that participated in the INPHARM study, Innlandet Hospital, Tynset, did not participate in the postal survey. Three hundred and twenty-two patients died before the survey, and 15 patients were excluded for miscellaneous reasons. A total of 548 patients were eligible and were sent a questionnaire, of whom 408 (74%) responded. In the retest we mailed a second questionnaire to 100 respondents 4 weeks after receiving their first response. The response rate in the retest was 81%.

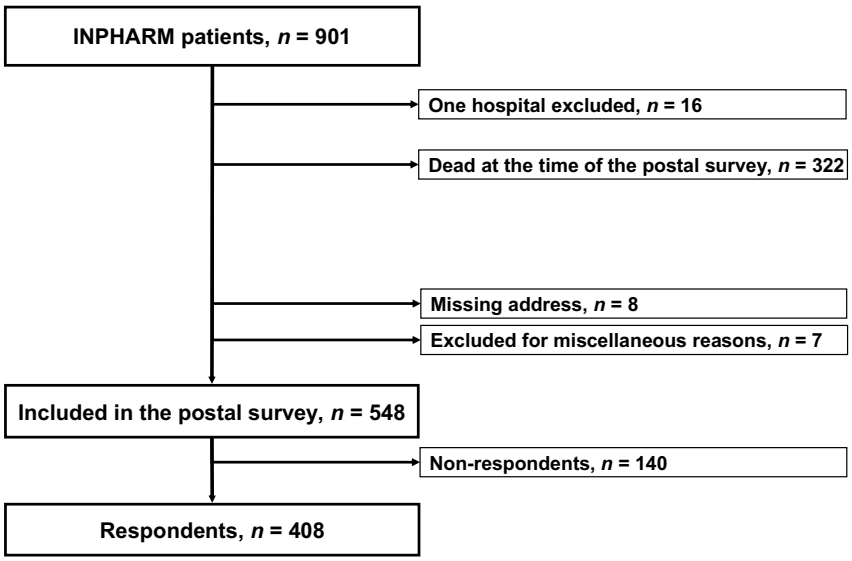

Figure 3 Material of the INPHARM study and the postal survey

3.3 Statistical analysis

We present descriptive statistics with mean and SD values or proportions, and for group comparisons we used *t*-tests, chi-square tests and Fischer's exact tests as appropriate.

Papers I and II describe how the test–retest reliability of the HRQoL scales in the KCCQ and the SAQ and summary scores of the KCCQ were determined using intraclass correlation coefficient (ICC) [79;146]. Test–retest analyses were performed using the scores of individual patient separated by a 4-week interval. We anticipated that the patients were in a stable phase and chose 4 weeks to minimize the recall of previous answers.

We assessed construct validity in Papers I and II by assessing intercorrelations of corresponding scales and summary scores. Construct validity would be supported by the correlation between scales measuring related phenomena being higher than that between unrelated scales. We quantified the correlation coefficients using previous nomenclature on agreement statistics: substantial (0.61–0.81), moderate (0.41–0.60) and fair (0.21–0.40) [147].

We assessed criterion-related validity by investigating the capability of the scales and summary scores of the KCCQ and SAQ to differentiate between groups defined by a criterion with expected differences in HRQoL. We used criteria from the literature, and general knowledge about and availability of disease characteristics to define groups. Paper I describes the use of medication at discharge that was prescribed for HF, and the LVEF as a criterion for assessing the validity of the KCCQ scales and summary scores. Paper II uses concurrent long-acting nitroglycerine and sublingual nitroglycerine as proxies for moderate and severe angina, respectively, as criteria for assessing the validity of the SAQ scales.

Papers III and IV use multiple linear regression to detect determinants of the two SF-36 summary scales, and of the KCCQ clinical summary and EQ-5D index, respectively. Papers III and IV use method enter and forward stepwise multiple regression analysis, respectively.

Paper III compare SF-36 scores in our sample of patients with previous MI with general-population norms [136]. To do this we computed new variables for each SF-36 scale for the individual patient, with these new variables being the difference between the observed score for each subject and the age- and sex-specific general-population norm. Comparisons with the general population were then performed using one-sample *t*-tests with Bonferroni corrections for multiple comparisons.

We compared scores on the HRQoL scale between groups of patients using analysis of covariance whilst adjusting for background variables such as age, sex and education.

Adjusted scores were presented as estimated marginal means. We used SPSS (SPSS, Chicago, IL) statistical software for all statistical analysis.

4 Results and general discussion

4.1 Summary of results

4.1.1 Paper I

Background: The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a recently developed disease-specific instrument for measuring health-related quality of life in patients with chronic heart failure regardless of aetiology.

Aim: To assess the reliability and validity of the KCCQ in patients with previous myocardial infarction.

Methods and Results: In 754 patients with myocardial infarction discharged alive, we collected clinical data from the patients' medical records. Two and a half years after the acute myocardial infarction, we mailed a self-administered questionnaire to the 548 patients still alive. The response rate was 74%. Internal consistency reliability, assessed with Cronbach's α, ranged 0.66-0.95. Test-retest reliability, tested with an intraclass correlation coefficient, ranged 0.41-0.83. The pattern of association between similar and dissimilar scales of the KCCQ and SF-36 supported the convergent/divergent validity of the KCCQ. Four of the KCCQ scales and the two summary scores discriminated between patients with and without medication for heart failure, and between different levels of left ventricular ejection fraction supporting different groups validity.

Conclusions: The Norwegian version of the KCCQ showed acceptable reliability and cross-sectional validity, which support the use of this questionnaire to measure health-related quality of life after myocardial infarction.

4.1.2 Paper II

The aim of this study was to validate the Norwegian version of the Seattle Angina Questionnaire (SAQ), a self-administered 19-item questionnaire designed to assess health-related quality of life in patients with chest pain or coronary artery disease. In 885 patients with prior myocardial infarction (MI), we abstracted clinical data from the patients' medical records. Two to three years after the MI, we mailed a self-administered questionnaire including the SAQ, the Short Form 36 (SF-36), and questions about current medication, to the 548 patients still alive. The response rate was 74%. Internal consistency reliability of the

SAQ, assessed with Cronbach's α, ranged 0.75–0.92. Test-retest reliability, tested with an intraclass correlation coefficient, ranged 0.29–0.84. The pattern of association between similar and dissimilar scales of the SAQ and SF-36 mainly supported the construct validity of the SAQ. Four of the five SAQ scales discriminated between patients with different medication regimens as a proxy for severity of angina pectoris. We conclude that the Norwegian version of the SAQ showed acceptable reliability and cross-sectional validity following MI, with properties in line with the original US version.

4.1.3 Paper III

Background: The role of sex differences in health-related quality of life (HRQoL) after myocardial infarction (MI) remains controversial.

Methods: In total 408 Norwegian patients completed the Short Form 36 (SF-36) questionnaire 2.5 years after MI. We compared HRQoL between sexes and with national norms. Multiple linear regression analysis was used to explore the association of scores on the Physical (PCS) and Mental (MCS) component summary scales with clinical and sociodemographic variables.

Results: Women scored lower than norms on the Physical functioning, Role functioning-physical, General health, and Role functioning-emotional scales. Men scored higher on Bodily pain, and lower on the other 7 scales compared to norms. Women <70 years scored lower than men on 3 out of 8 scales and on PCS. Women ≥70 scored lower than men on 5 out of 8 scales and on PCS. Relative to sex- and age-specific norms, there were no sex-differences in SF-36 scores. Age, time since the index MI, chronic obstructive pulmonary disease (COPD), previous MI, and stroke predicted PCS scores in women. Education, COPD, infarct localization, number of indications for cardiovascular medication at discharge, medication for heart failure, and subsequent MI predicted PCS scores in men. Smoking status, education, and Q-wave MI were determinants for MCS scores in men.

Conclusion: Patients had impaired HRQoL compared to sex- and age-specific norms 2.5 years after MI. Women had lower HRQoL scores than men, but relative to norms HRQoL was equally affected in both sexes. Men and women had different determinants of HRQoL.

4.1.4 Paper IV

Background: The objective was to explore the relationship between left ventricular ejection fraction (LVEF) assessed during hospitalization for acute myocardial infarction (MI) and later health-related quality of life (HRQoL).

Methods: We used multivariate linear regression to assess the relationship between LVEF and HRQoL in 256 MI patients who responded to the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EQ-5D 2.5 years after the index MI.

Results: 167 patients had normal LVEF (>50%), 56 intermediate (40%–50%), and 33 reduced (<40%). The mean (SD) KCCQ clinical summary score was 85 (18), 75 (22), and 68 (21) ($p<0.001$) in the three groups, respectively, and the corresponding EQ-5D Index scores were 0.83 (0.18), 0.72 (0.27), and 0.76 (0.14) ($p=0.005$). In multivariate linear regression analysis age ≥70 years, known chronic obstructive pulmonary disease, subsequent MI, intermediate LVEF, and reduced LVEF were independent predictors of reduced KCCQ clinical summary score. Female sex, medication for angina pectoris at discharge, and intermediate LVEF were independent predictors of reduced EQ-5D Index score.

Conclusions: LVEF measured during hospitalization for MI was a predictor for HRQoL 2.5 years later.

4.2 Methodological considerations

4.2.1 Patients

The patient sample in the INPHARM study can be regarded as representative of Norwegian MI patients, since consecutive MI patients were included, hospitals recruited patients over similar time periods and a wide range of hospitals (both teaching and non-teaching) in different geographic regions participated. Also, the 548 patients included in the postal survey were regarded representative of patients surviving 2–3 years after their MI.

Table 2 in Paper I compares respondents and non-respondents in the survey. Non-respondents were more likely to be female, and were older, had more cardiovascular diagnoses before the index MI and were discharged with less medication primary prescribed for secondary prevention and more medication prescribed for HF. Also, the LVEF tended to be lower in non-respondents. These results indicate that the CVD burden was higher for non-

respondents than for respondents, which might have influenced the HRQoL scores, especially on scales assessing physical health.

Our response rate of 74% is comparable to response rates of 74–89% in other studies [38;114;115;118;119;121;148]. The two studies with the highest response rates used the SF-36 2 and 4 years after an index MI [38;115]. The youngest patients in our study scored higher and the older patients comparable to age-matched patients in the study that assessed HRQoL 4 years after MI [38], and the scores of our patients were comparable to patients in the study on HRQoL 2 years after MI [115]. However, the latter study included only patients with a first MI [115].

4.2.2 Design and data collection

While the INPHARM study was a cross-sectional survey, the follow-up study was a prospective observational cohort study [149]. However, we only assessed HRQoL in the patients once. We do know the HRQoL of the patients at a mean of 2.5 years after the index MI, but we do not know their HRQoL prior to the MI. Therefore, we do not know the changes in HRQoL. To determine whether there is a causal relationship between determinants and HRQoL, such possible determinants should be related to changes in HRQoL between before and after the MI. The time lag between the clinical variables registered at the time of the MI and assessment of HRQoL has implications for the direction of an observed association. For example, a reduced HRQoL does not cause a reduced LVEF.

When we planned the study, there were reports on HRQoL at 6 months, 1 year, 2 years, 4 years and 5 years after an index MI, but no studies for the period between 2 and 4 years [36;38;118;120;122;127;148]. At 2 to 3 years after the MI we would expect the patients to be in a stable phase, and that most of the expected improvement after the MI was achieved.

In the INPHARM study, local physicians collected clinical data, data on in-hospital treatment and medication at discharge, and the study thus involved several persons, most of who were cardiologists. All of the physicians had experience in handling heart patients and were familiar with the local medical records, routines and guidelines, which should have improved the completeness and reliability of the data. Information on the indication for drug use at discharge was also collected from the medical record, but this is not always clearly stated in a patient's records. Many cardiovascular drugs have more than one indication for use. The main indication for use was sought, but identifying this retrospectively can be difficult and require interpretation by the individual clinician.

In the postal survey patients reported their medication use in the questionnaire. We did not compare this with drug lists in the hospital records. However, a recent study found good agreement between patient-reported medication use and information in their medical records [150].

The hospital diagnosis of MI was accepted without reassessment or revision, and all hospitals used the same definition of acute MI [4]. The criteria for diagnosing MI were changed in 2000, shortly after the patients in our study had been diagnosed. The new MI definition has placed more emphasis on biochemical markers and less on clinical parameters and ECG, which has resulted in an increased incidence of small MIs, with some patients who had previously been diagnosed as unstable angina or angina pectoris now being diagnosed as MI. It is not obvious how this change in patient population has influenced HRQoL among MI patients. In a study on HRQoL in ACS that analyzed patients in 1998 and 1999 (and thus using the same definition for acute MI as in the present study), a discharge diagnosis of unstable angina was a predictor of a reduced SF-36 PCS score [151]. To my knowledge, no reports on intermediate- or long-term HRQoL after MI using the new diagnostic criteria have been published so far.

4.2.3 HRQoL instruments

There are disease-specific instruments such as the MacNew QLMI questionnaire that cover the major domains of HRQoL following MI without reporting HRQoL separately with regard to the most common heart-specific complications following MI; that is, chest pain or HF [102]. To improve the relevance of our study to clinical cardiology, we decided to use separate instruments for HF and angina pectoris, and chose instruments that included the symptom frequency and severity. Frequently MI also affects mental well-being. Therefore, to cover most of the effects of an MI on the health status, we also included an instrument assessing mental health status. We chose the Hospital Anxiety and Depression scale, which is a 14-item self-administered instrument assessing anxiety and depression in patients with somatic diseases [152]. This scale has been translated into Norwegian and used in patients with heart diseases [153-155]. The SF-36 was the first-choice generic instrument, since it is widely used, has high reliability and validity in patients with CAD, and reference values are available for a Norwegian general population [97;136]. The second generic instrument included in the questionnaire, the EQ-5D index, was attractive due both to its brevity and the

possibility of converting it into a utility score [137;139;156]. EQ-5D has also been found to be reliable and valid in patients with MI [99].

The SAQ, KCCQ and SF-36 are all HRQoL instruments covering the most common domains of HRQoL. Combining these instruments in the same questionnaire provided detailed information on how angina pectoris, HF and general health affect HRQoL after MI, with the possibility to compare and analyze differences and variations. However, we do not know how repeated questions on the same subjects influence the responses, even though the patients were told to consider each item with regard to chest pain or HF, for example.

4.2.4 Statistical considerations

It has often been discussed whether to use parametric or non-parametric statistical methods when investigating quality of life. The individual item responses collected in assessments of HRQoL are most often ordinal or nominal data. Such item responses are often aggregated to scales, which are analyzed further with the assumption that the aggregates now have interval properties and are normally distributed. This can be an invalid assumption. Some of the non-parametric methods are difficult to apply, and hence researchers often use standard parametric methods. This is also the case in other areas of research in medicine and psychology. A survey of 175 papers using ordinal data found that at least 75% of them used statistical methods that assumed a measurement scale with interval or ratio properties [157].

How to specify models in multiple regression analysis and whether it is feasible to use automated models for variable selection also needs to be considered [158]. Paper III describes the manually building of multivariate models based on a-priori-determined criteria. Paper IV describes stepwise forward variable selection. In both instances variables were restricted in advance, based on findings in the literature and on their availability in our sample.

4.2.5 Ethics

Both the INPHARM study and the HRQoL postal survey were approved by the Regional Committee for Medical Research and the Norwegian Data Inspectorate. The data in the INPHARM study were collected after the patients were discharged. Therefore, none of the clinicians was aware of the study when patients were in hospital for their index MI. Thus, the INPHARM study did not interfere with in-hospital treatments of MI. However, the design of the study did not allow patients to exclude themselves from the cohort.

Patients were not aware of the HRQoL postal survey before they received an invitation to participate and orientation about the survey signed by the head of the cardiology section or department together with a supplementary letter from the researchers and the questionnaire. Therefore, the invitation to participate in the survey could have been an unpleasant reminder of what the patients might have regard as a closed book, especially for those without symptoms from their CAD and with normal physical function. However, the high response rate indicates that this approach was generally accepted.

A few of the questionnaire items could have been regarded as offensive by some patients, such as item 15 in the KCCQ that asks about "intimate relationships with loved ones". This or other items could have led to patients feeling that their privacy was violated, resulting in them not returning the completed questionnaire or not responding to that specific question. Indeed, only 28% of our respondents provided a valid response to this item. The rate of single-item non-response was 10–16% on three other items asking about working-, leisure- and social activities.

4.3 Discussion of the main results

4.3.1 Reliability and validity of the instruments

As expected, the patients in our study scored substantially higher on all KCCQ scales, and had a relatively high ceiling effect (13–36%) on the different scales compared to patients with known HF [106]. Our patients also scored higher than patients with stable angina on four out of five scales of the SAQ [103;159]. One of the inclusion criteria in the study of angina pectoris by Spertus et al. was current prescription of nitroglycerine [103]. The scores on the SAQ scales of patients in that study were comparable to the scores of those patients in our study who reported that they used nitroglycerine (Table 5 in Paper II). Acceptability of the translated instruments among patients in our study was satisfactory, with >90% and 89–97% scorable multi-item scales for the KCCQ and SAQ, respectively. In our study the internal consistency reliability of the KCCQ scales equaled that of the original version of the KCCQ, with values of >0.70 on all scales except Self-efficacy. For the Norwegian translation of the SAQ, all the Cronbach's α values were >0.80. The test–retest reliability as quantified by ICC for the KCCQ was >0.70 on all scales and summary scores except Symptom stability, Self-efficacy, and Quality of life. The ICC was >0.70 on all scales of the SAQ except Angina

stability. It has been suggested that HRQoL instruments can be used for comparisons at the group and individual patient levels when the reliability is >0.70 and >0.95, respectively [79;160]. Acceptable reliability for comparisons at the group level were obtained when these criteria were applied to the Norwegian translations, the SAQ scales Physical limitation, Angina frequency, and Treatment satisfaction, and the KCCQ scales and summary scores Physical limitation, Symptoms, Social limitations, KCCQ Functional Status, and KCCQ Clinical Summary. However, none of the scales fulfilled the criteria for use at the individual level.

The discriminatory capacity was higher for the KCCQ than for the generic SF-36 instrument for all scales except the Symptom stability and Self-efficacy. However, the SF-36 has a broader scope, and hence supplements the KCCQ. These results support the construct validity of both the KCCQ and SF-36 in patients with previous MI. The SF-36 has previously shown high validity in patients with CAD, but this has not been tested for the Norwegian translation [97]. The KCCQ was developed in patients with HF but is relevant to a substantial proportion of MI patients, and our results support its validity in unselected patients with previous MI.

We assessed convergent/divergent validity, which is an aspect of construct validity, using a multitrait-multimethod matrix. For the KCCQ all predicted substantial correlations between KCCQ scales and summary scores and SF-36 scales were ≥0.56. The criterion for a substantial correlation is considered to be 0.60, and this was satisfied for 16 of the 20 predicted correlations [147]. For the SAQ, 9 of the 13 predicted correlations were >0.54 and 6 were >0.60. We used medication for HF at discharge and current antiangina medication as criteria for different group validity [161]. All scales and summary scores of the KCCQ except Symptom stability and Self-efficacy performed well, as did all SAQ scales except Angina stability, indicating high validity of the two instruments.

Our cross-sectional study could not assess responsiveness. The KCCQ has been shown to have better responsiveness than the MLHF and to reflect clinical changes in HF patients better than the NYHA classification and 6-minute walk test [106;162]. However, the responsiveness of the KCCQ needs to be assessed also in patients with previous MI. The SAQ has been shown to be responsive in patients with CAD, but like the KCCQ needs to be tested separately in patients with MI [103;140].

4.3.2 Comparisons with the general population and patients with other diseases

The scores of our patients were significant lower than those of sex- and age-adjusted norms on all SF-36 scales except Bodily pain (Table 3 in Paper III) [136]. A difference in score of 5 or more on the SF-36 scales from 0 to 100 is often regarded as clinically significant [133]. Applying this criterion conservatively, we found a clinically significant reduced score on the scales of Physical functioning, Role functioning–physical, General health and Role functioning–emotional. However, the scores exhibited only moderate differences between our patients and the general-population norms, being less than 10 on most scales. Still, given the high prevalence of previous-MI patients in the general population, a reduced HRQoL in MI patients represents a substantial societal health problem.

The difference in score between previous-MI patients and norms was generally the same in both men and women, and in patients below and above 70 years. Our results are consistent with most studies finding that MI reduces HRQoL compared to norms, at least until 5 years after the index MI [38;113-116;163].

The differences in SF-36 score between previous-MI patients and sex- and age-adjusted norms in our study were smaller than the differences reported by Brown et al. in MI patients younger than 65 years assessed 4 years after their index MI [38]. The patients in that study had experienced their index MI approximately 7 years before the patients in our study, and during which drug therapies improved and aggressive interventions became more common [17]. This might have contributed to the better results in our study.

HRQoL scores in patients with cardiovascular conditions are reported to be comparable to those for other chronic conditions such as cancer and chronic respiratory diseases, but higher than those in patients with musculoskeletal, renal, gastrointestinal, cerebrovascular or neurological conditions [38;113-116;163].

4.3.3 Determinants of HRQoL

Different determinants and predictors of HRQoL following MI have been identified. The predictors have varied between studies depending on factors such as patient selection, the possible predictor variables included, the applied HRQoL instrument and the time interval between the index MI and HRQoL assessment.

In a systematic review on 11 studies published before 1999, Simpson and Pilote found that the most significant predictors of HRQoL after MI were the severity of persistent symptoms such as dyspnoea or chest pain, the patient's age, and the timing of HRQoL measurements [109]. Two more recent studies by Beck et al. (on patients with MI) and Rumsfeld et al. (on patients with ACS) both concluded that non-cardiac factors were the most powerful predictors of subsequent HRQoL [118;151]. The latter study measured HRQoL 7 months after the index hospitalization, and identified both previous CVD (e.g. prior CABG surgery and HF) and also non-CVDs such as depression, arthritis, COPD (chronic obstructive pulmonary disease), diabetes mellitus, previous peptic ulcer disease, reduced kidney function and stroke as predictors of HRQoL as measured by the SF-36 PCS or MCS [151]. They also identified revascularization – both during the index hospitalization and after discharge – as positive predictors of HRQoL. Beck et al. measured HRQoL both during hospitalization and after 1 year, with the baseline HRQoL used as an independent variable in the analysis of determinants for HRQoL [118]. In addition to baseline HRQoL, only age, sex and previous CABG surgery were associated with the PCS score at 1 year. The presence of depression at the time of the index MI was the only predictor of MCS other than the baseline score. Including baseline HRQoL in the analysis accounted for much of the comorbidity that otherwise might have been an important predictor. This latter study actually analyzed predictors of recovery after MI. The social network has also been identified as a predictor of the long-term MCS score [121].

The design of our study was the same as that of Rumsfeld et al., with HRQoL measured once only, and thus HRQoL in our study might have been affected by previous health conditions, factors associated with the index MI, and subsequent events [151]. We applied separate analyses to men and women (Table 4 in Paper III), which indicated that the predictors among men were the total number of indications for cardiovascular drugs at discharge and medication for HF at discharge. The number of cardiovascular indications for treatment at discharge was influenced both by previous CAD and the index MI, which cannot be distinguished. In women, previous MI, previous stroke and COPD were all associated with a lower PCS score.

Among men, there was a clinically and statistically significant association between localization of the index MI and long-term HRQoL [133]. To our knowledge no previous study has shown this association, possibly because none of them applied separate analyses to the two sexes. Alternatively, a separate underlying cause (e.g. undetected previous MIs) could explain both the difficulty of localizing the index MI and the reduced HRQoL. In men,

but not in women, subsequent MI was associated with a reduced PCS score. However, this might be related to reduced statistical power, as only 3% of the women in our study reported new MIs.

In our study age was associated with HRQoL only in women (Table 4 in Paper III). This was somewhat surprising considering that in the Norwegian national norms there is an age-related decrease in score on the four SF-36 scales that is associated most strongly with physical health, with the decrease appearing in the sixth decade in men and in the seventh decade in women [136]. This age-dependent decrease in HRQoL in the general population might be attributable to ageing per se, due to decreased physical capacity, increased total burden of disease or reduced social support [131;164]. In addition, elderly subjects with MI have increased incidences of pre-MI CAD, reduced heart function, atrioventricular conduction disturbances, atrial fibrillation and diabetes mellitus, all of which might affect HRQoL. The age-dependent decrease in HRQoL in the general population indicates that not evaluating age as a determinant of HRQoL in patients with MI might lead to an overestimation of the effect of an MI in elderly patients or an underestimation of the effect in younger patients.

4.3.4 Sex difference in HRQoL after MI

We observed that the unadjusted HRQoL scores differed between men and women (with the lowest scores in women) on many of the SF-36 scales both for patients younger and older than 70 years (Table 2 in Paper III). There are at least three theoretical health-related explanations for a sex difference in HRQoL scores after MI [165]. First, they might be due to CAD being more severe in women than in men. Second, women might have more premorbid comorbidities or a lower functional level, with the observed differences thus being due to existing sex differences in the general population. Third, women might have poorer recovery after an MI compared to men, which is supported by one study finding that the recovery in the first year after an MI was worse in women than in men on several SF-36 scales [166]. A fourth, more methodological explanation of observed sex difference in HRQoL is that the employed HRQoL instrument favours aspects of HRQoL for which men generally have a higher functional level than women. For example an instrument which emphasizes physical function and symptoms would lead to this type of sex-difference. Men generally have higher physical function than women, and it has been suggested that men are socialized to ignore physical discomfort and thus are unaware of symptoms women feel keenly [167]. There is

research evidence supporting all of the health-related explanations. CAD is diagnosed later in women than in men, and therefore women have a longer period without treatment, which would result in a more severe status when the condition is finally diagnosed.

When interpreting observed sex differences in SF-36 scores in patients, it must be noted that men in the general population score higher than women at the same age on most SF-36 scales [133;136]. We accounted for this sex difference in general-population norms when comparing scores on SF-36 scales between male and female patients by computing new variables for each SF-36 scale defined as the difference between the observed score for each respondent and the age- and sex-specific general-population norm. Applying these new variables revealed no sex difference in scores on SF-36 scales in post-MI patients beyond the sex difference in the general population, and hence the sex differences in scores on SF-36 scales in our study are likely to simply reflect differences in the general population.

4.3.5 LVEF and HRQoL

The LVEF is an important predictor of survival in patients with heart disease and is the most commonly used non-invasive measure of cardiac function [31;168;169]. The LVEF is a measure of left ventricular systolic function, with its value being an important indicator of the amount of heart muscle loss during an MI. However, other factors such as diastolic function, valvular heart disease, dyssynchronicity or arrhythmias can all impact on the overall function and physical capacity of the heart. More composite measures of a patient's physical function, such as a 6-minute walk test, will be influenced by lung function, muscle strength and diseases affecting the locomotor system. Similarly, these conditions will also influence the NYHA classification. Further, physical functioning is only one of multiple domains contributing to the construct HRQoL. Therefore, the association between the LVEF and HRQoL is not obvious, and this explains why studies involving patients with previous MI both have and have not observed an association between the LVEF and HRQoL [115;117;119;170-177].

In our study we identified a moderate but highly statistically significant association between the LVEF measured during hospitalization for the index MI and HRQoL about 2.5 years later, after controlling for other variables (Table 3 in Paper IV). A moderate association between the LVEF and HRQoL would be expected from the conceptual model of Wilson and Cleary [70] that illustrates the presence of multiple links between physiological measures and HRQoL, and hence that HRQoL can be influenced by diverse factors.

4.3.6 Limitations

In each of Papers I–IV we have reviewed the limitations of the analyses and the uncertainty of the study, including the response rates, the possibility of multiple indications for cardiovascular drug treatment at discharge, the use of different methods to assess the LVEF and problems with reliability when data were collected by multiple clinicians. Other limitations relate to the study design with HRQoL measured once only.

The change in the diagnostic criteria for MI in Norway in 2000, lead to an increased number of MIs being diagnosed. The disease entity ACS – which comprises ST-segment elevation MI, non-ST-segment elevation MI and unstable angina – is increasingly used in clinical practice. Caution is required when generalizing results obtained in patients diagnosed according to the WHO definition to patients diagnosed with the new MI criteria or to patients with ACS.

5 Conclusions and future perspectives

5.1 Conclusions

- This study has validated the Norwegian translations of two heart-specific HRQoL instruments, which will facilitate the use of these instruments in Norwegian patients without a long documentation process. Our results also support the validity of the Norwegian translation of the SF-36 in patients with previous MI.
- We have identified that HRQoL in both men and women is lower about 2.5 years after an MI than in age- and sex-matched Norwegian norms.
- Given the existing difference in scores between men and women in the general population, HRQoL was equally affected after MI in the two sexes. This implies that caution is required when directly comparing HRQoL between the sexes.
- We have presented and applied a statistical method for comparing SF-36 scores between groups of patients that takes into account general-population scores.
- We have demonstrated that HRQoL about 2.5 years after an MI is more closely associated with features of the index MI in men than in women.
- In patients with acute MI, heart function during hospitalization – as measured with the LVEF – showed a moderate but statistically significant association with long-term HRQoL.

5.2 Future perspectives

While the original SAQ and KCCQ have shown good results [103;106;140], the responsiveness of their Norwegian translations needs to be tested, such as in stable angina patients undergoing planned PCI and in HF rehabilitation clinics, respectively.

To facilitate the use of HRQoL measures in clinical practice, it would be useful to have instruments that can be applied longitudinally to individual patients. HRQoL measures need to exhibit sufficient validity and reliability in individual patients before they can be used in clinical practice. Applying HRQoL regularly to individual patients will improve the accuracy of doctor–patient communications and thus could contribute to improved treatment. The

further development of instruments to achieve this should be a top priority of HRQoL research in patients with CAD.

Whether future studies should use generic or disease-specific HRQoL instruments depends on the purpose of each study. When assessing the effect of an intervention it is feasible to use measures that are most sensitive to change, which frequently is a disease-specific instrument. However, generic measures must be used if the purpose is to compare patients with different diseases or with the general population. Often a survey aims at both, and hence a common recommendation is to use both a generic and a disease-specific instrument.

Wilson and Cleary have presented a general conceptual model linking clinical variables with HRQoL that takes into account characteristics of the individual and the environment [70]. This model can serve as a basis for testing the relationship between sets of clinical variables, measures of heart function and HRQoL in patients with CAD. Formally testing an a priori model in any appropriately designed study will improve the knowledge of how potential determinants of HRQoL relate to different aspects of HRQoL and quality of life, and also how the determinants are interrelated. A better understanding of the interrelation of possible predictors of HRQoL could lead to an increased awareness of potentially modifiable determinants, better tailored treatment and at the same time a more holistic care for patients with CAD.

HRQoL has been found to be a predictor of survival in patients with heart disease [87;142;178;179]. A better understanding of the association between HRQoL and survival could contribute to improved treatment. For example, will treatments that improve HRQoL also improve survival?

The new diagnostic criteria for MI have reduced the distinction between MI and unstable angina, and the term ACS is now more commonly used. A longitudinal cohort study comprising a broad spectrum of ACS patients and with the intention to measure both the short- and long-term HRQoL, together with death and hospital admissions, would be very useful for understanding all aspects of the course of ACS.

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